Remarks

Claims 2 and 7 to 18 are pending and before the Examiner. In response to the prior Appeal Brief, the Examiner has reopened prosecution with new rejections. Applicants have elected to respond to the Office Action below to narrow the potential issues for subsequent appeal, which seems to be necessary.

The Examiner again rejected claims 2 and 7 to 13 as allegedly failing to provide enablement under 35 U.S.C. § 112, first paragraph, for the prevention of the recited conditions.

In response, applicants again traverse the rejection of the claims directed to prevention as improper. "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement". *In re Wright*, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)(emphasis added).

As pointed out previously, the specification makes clear that one aspect of the invention is providing the ability to treat patients before they may be officially diagnosed with the stated condition (see, e.g., page 7, lines 13-15; page 8, lines 29-30; page 10, lines 19-20; page 13, lines 8-11; page 14, lines 19-31; page 18, lines 24-26, discussing the ability to use the method to treat "first indications" of the conditions, pre-diabetes or patients "suspected of" the conditions). Further, it is also clear that an aspect of the invention is treating patients based on observance of certain physiological parameters (see, e.g., claims 8-11) even absent an official diagnosis of the condition (see also page 12, lines 5-10). Thus, in order to properly claim their invention it is necessary in this context for applicants to claim a method for "prevention or treatment" of the recited conditions. The specification teaches one of ordinary skill in the art how to provide and administer the compositions, as explained in more detail below.

The Examiner has clarified that the rejection is based on a requirement that the term "prevention" does not require that the method result in 0% occurrence of the condition and a

guarantee that the condition would never develop, but has not explained what the criteria for establishing prevention is.

The Examiner refuses to follow *Ex parte Cho*, Appeal No. 2001-2646 (Bd. Pat. App. & Int. 2002), arguing that the Examiner has somehow distinguished *Cho* and pointing out that it is nonprecedential. Applicants disagree and maintain that the distinctions between *Ex parte Cho* and the instant situation are insubstantial and *Ex parte Cho* should be followed because it is an example of how the law is correctly applied. *Ex parte Cho* addressed the issue of enablement of claims which encompassing "preventing" and "treating"; as in the instant case, that rejection indicated that the claim scope encompassing treating was enabled but the inclusion of preventing supported a non-enablement rejection. Thus, the case is directly on point with the facts in the instant case. Notably, the Board reversed the Examiner's rejection stating (page 7):

> "Logically, if the recited compounds are useful for treating conditions such as pain and inflammation once they exist, they would also be expected to be effective in preventing pain and inflammation, if they were administered before the onset of pain or inflammation. The examiner has provided no reasoning to support a contrary conclusion" (**emphasis in original**).

The same logic applies here and the examiner has also provided no reasoning to support a contrary conclusion here. The Examiner merely provides the allegation that, because metabolic syndrome is "complex", there is significant doubt whether a compound established to treat metabolic syndrome is also capable of preventing it. Applicants submit that the above discussion provides sufficient reasons for reversing the rejection.

Applicants additionally differ with the Examiner on the Wands factors (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) as applied to the instant claims, which are discussed below as further proof of the adequate enablement of the claims.

The Breadth of the Claims – The breadth of claims, on appeal, is quite narrow. The claims are directed to methods for treatment or prevention of a specified group of nine related conditions using a highly specific composition which combines two specific active agents. The narrow breadth of the claim strongly supports adequate enablement.

The Nature of the Invention – There has been no allegation in the Office actions of how the nature of the invention supports lack of enablement. In the absence of any apparent reason why the nature of the invention supports lack of enablement, this factor also must be considered as supporting a finding of enablement.

The Level of One of Ordinary Skill in the Art – The level of skill of one of ordinary skill in the art providing pharmaceutical compositions and methods for treating life-threatening conditions in humans is very high. The level of skill in this art would generally be that of a Ph.D. research chemist with years of experience. This high skill level strongly supports a finding of enablement.

The State of the Prior Art and Level of Unpredictability in the Art – The standard for enablement is not absolute predictability but only reasonable expectation of success; see *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510,1512 (Fed. Cir. 1993). On this issue, the only evidence the PTO has relied on to support the case for lack of enablement is the Grundy ("Metabolic Complications of Obesity") article. The article is relied on for its statement that treating or preventing the metabolic syndrome condition (one of the conditions recited in the claims) is "complex" (see, e.g., page 3 of the Final Office action). In fact, Grundy does not state that treating or preventing this condition is complex. Instead, the article is directed specifically to the role obesity plays in the condition and states that the "mechanistic link between insulin resistance and metabolic syndrome is complex" (see the abstract of Grundy). The article then goes on to describe in great detail how the metabolic syndrome condition is characterized and how a number of factors affect the condition. Thus, while acknowledging the complexity, it also acknowledges that much is known about the causes and many aspects of the condition. The fact that the condition may be complex does not support lack of enablement when – although complex – it is well understood by one of ordinary skill in the art. The grounds of rejection fail to explain why the complexity of the condition supports that one of ordinary skill in the art could not carry out the claimed method given the high level of knowledge in the art and direction given in the disclosure of the details of administering the compositions to carry out the method. Given that the claimed method of treatment of metabolic syndrome is admitted to be enabled, it would follow that the method of prevention of metabolic syndrome would also be enabled regardless of the alleged "complex" nature of

the syndrome. As discussed above, the difference in carrying out the method of treatment or prevention is merely one of timing. The Grundy article also states (abstract) that "at the heart of metabolic syndrome is insulin resistance." This fact closely ties the method of treating or preventing this condition with the method of treating or preventing the other conditions to which the claimed methods are directed, e.g., insulin resistance, prediabetes and type 2 diabetes. The Examiner has not provided any evidence or argument that treating or preventing these other conditions is not enabled. But the close tying of metabolic syndrome with these conditions would support that, if treating or preventing the other conditions is enabled, then treating or preventing metabolic syndrome would also be. The abstract of the Grundy article concludes that a "better understanding of the molecular basis of this relationship [i.e., the mechanistic link between insulin resistance and metabolic syndrome] is needed." Again, this statement relates only to this particular relationship. Further, the fact that a journal article concludes that a better understanding is needed does not prove that one of ordinary skill in the art could not carry out methods to treat the condition. Journal articles usually conclude in this manner because researchers are always looking for a better understanding. This does not evidence that the current understanding is insufficient for one of ordinary skill in the art to carry out methods to treat the condition. Obviously, researchers are always searching for improved ways to treat conditions despite that existing methods for treating them may already be well known. Applicants additionally point out that the principle and closest prior art reference cited in the obviousness rejection, DeGasparo also recites that its methods are for prevention or treatment of the conditions recited there (see page 1, line 8). Thus, this closest prior art is consistent with applicants' position that this specific art area is directed to treatment and prevention of the conditions.

The Amount of Direction Provided – The specification provides a great deal of guidance on how to carry out the claimed invention, including for the prevention aspect. The discussion in the first paragraph above for this issue is referred to, pointing out that the specification makes clear that aspects of the invention include providing the ability to treat patients before they may be officially diagnosed with the stated condition, to treat "first indications" of the conditions, pre-diabetes or patients "suspected of" the conditions, and further, treating patients based on observance of certain physiological parameters even absent an official diagnosis of the condition. The disclosure thus addresses methods encompassing the spectrum spanning preventing and treating the stated conditions. Furthermore, the

specification provides a great deal of guidance on how to administer the specifically identified compositions that result in the method. For example, pages 9-14 and 20-27 of the specification give a wealth of information on assays for assessing the desired activity of the compositions, physiological parameters for identifying patients in need of the method, manners of formulating the compositions, suitable methods for administering the compositions and specific doses of the active agents in the compositions. From such guidance, one of ordinary skill in the art – who is of a very high skill level – can routinely carry out the claimed invention.

The Existence of Working Examples – It is well established that no working examples are required to establish enablement; see, e.g., *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). This is commonly the case for medical treatment methods where clinical work is not performed until later in the development path.

The Quantity of Experimentation Needed – The requirement for some experimentation – even a large amount – does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., *In re Wands*, at 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also *Ex parte Jackson*, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." As stated above, the experimentation needed by the highly skilled one of ordinary skill in the art here would only be routine. Considered as a whole, applicants maintain that the Wands factors clearly support that the claims are reasonably enabled. Accordingly, the specification, read in light of the knowledge available to one of ordinary skill in the art,

provides an adequate disclosure or how to make and use the invention of the claims. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner again rejected claims 2 and 7 to 18 as allegedly unpatentable under 35 U.S.C. § 103(a) over De Gasparo *et al.*, in light of Robl *et al.* (cited to show a fact), in light of Weinan *et al.*, Card. Drug Rev. 18(2), in view of Cecil's Textbook of Medicine (2000), Harlan *et al.* (U.S. Patent Appl. Pub. No. 2001/0006656), and Bohm *et al.* (WO 02/15891).

Applicants again respectfully traverse the rejection. De Gasparo *et al.* does not specifically disclose the specific combination of telmisartan and atorvastatin anywhere, as the Examiner acknowledges. The teachings and statements in De Gasparo *et al.* must be considered in context and interpreted as a whole. De Gasparo *et al.* discloses a combination of angiotensin II receptor blockers and HMG-CoA reductase inhibitors, which in general encompasses, but does not teach or disclose, the combination of telmisartan and atorvastatin. De Gasparo *et al.* does not disclose a specific technical teaching which would suggest to the person skilled in the art to select telmisartan from among the various sartans mentioned or even give any technical preference to one of the various combinations suggested. De Gasparo *et al.* thus generally offers the options of:

(a) AT_1 receptor antagonist + HMG-Co-A reductase inhibitor;
(b) AT_1 receptor antagonist + ACE inhibitor
(c) AT_1 receptor antagonist + HMG-Co-A reductase inhibitor + ACE inhibitor;
(d) AT_1 receptor antagonist + diuretic + HMG-Co-A reductase inhibitor;
(e) AT_1 receptor antagonist + diuretic + ACE inhibitor; and
(f) AT_1 receptor antagonist + diuretic + HMG-Co-A reductase inhibitor + ACE inhibitor.

In contrast, the present invention is based on three important selections for which there is no guidance in De Gasparo *et al.* First, the specific combination type of AT_1 receptor antagonist + HMG-Co-A reductase inhibitor is selected. Second, the selection of telmisartan as the AT_1 receptor antagonist, which is shown for the first time to have a uniquely strong effect on genes regulated by the PPARgamma receptor, a receptor which was known to the person skilled in the art to interfere with lipid and glucose metabolism is made. This

unexpected effect of the specific AT_1 receptor antagonist telmisartan makes telmisartan a particularly preferred combination partner for lipid lowering HMG-Co-A reductase inhibitors. Third, the selection of atorvastatin as the HMG-Co-A reductase inhibitor is made. Atorvastatin shares with telmisartan lipophilic properties which are combined with a comparably long half life of 14 hours. These selections are not advocated by De Gasparo *et al.*

De Gasparo *et al.* does not give any preference to any particular combination within the broad disclosure, certainly not a specific combination of telmisartan and atorvastatin. Indeed, De Gasparo *et al.*, at page 3, line 22, merely defines "AT_1 receptor antagonists" as including a number of commercially available sartans including telmisartan, which is not disclosed as a selected compound in the context of a specific combination, much less with atorvastatin. The only sartan specifically mentioned in De Gasparo *et al.* in the context of a specific combination is valsartan which actually teaches away from telmisartan as a preferred combination partner. Similarly, in De Gasparo *et al.*, atorvastatin is mentioned on page 5, lines 6 and 10, but not in the context of a specific combination, much less with telmisartan. On page 5, line 26, De Gasparo *et al.* teaches that atorvastatin is a preferred composition partner with valsartan (not telmisartan) again teaching away from telmisartan as a preferred combination partner of atorvastatin. Instead De Gasparo *et al.* on page 6, line 8 refer to a combination of statins such as atorvastatin with ACE inhibitors while there is no analogous teaching with regard to AT_1 receptor antagonists at all. The Examiner argues that this does not amount to a teaching away from the claimed invention, but applicants respectfully disagree if the full context is considered.

Furthermore, none of Weinan *et al.*, Robl *et al.*, Cecil's Textbook of Medicine, Harlan *et al.*, or Bohm *et al.* provide what De Gasparo *et al.* lacks in providing to one of skill in the art as a motivation, reasonable expectation of success, or teaching or suggestion of all of the claim limitations of the claimed invention. This is explained in more detail below.

First, Robl *et al.* does not teach structures which encompass atorvastatin, does not teach combinations of atorvastatin with any compound except for the class of HMG-CoA reductase inhibitors claimed, and does not even mention telmisartan.

Second, Weinan *et al.* is limited to discussing characteristics of telmisartan and monotherapy. The various advantages of telmisartan mentioned by the Examiner in the rejection did not make telmisartan the most prescribed sartan for hypertension, which undercuts the Examiner's entire line of argumentation of the clear superiority of telmisartan, even more as a combination partner. Instead, there existed and exist different views of skilled artisans as to the preferable sartan to treat hypertension. Since this is obviously true for the monotherapy of hypertension, it is respectfully submitted that this would be particularly true for a combination therapy with atorvastatin. In contrast to what was known in the prior art, the claimed invention unexpectedly and surprisingly found that, compared to the other sartans, telmisartan has a particularly strong interaction with the metabolic target of the PPARgamma receptor, which by a considerable number of skilled artisans is recognized as making telmisartan the preferable sartan combination partner for the HMG-CoA reductase inhibitor atorvastatin, a combination that was not specifically motivated or suggested by the prior art.

Third, the teaching of Harlan *et al.* is confined to aerosol formulations of statins: such formulations are not intended to combine a statin such as atorvastatin with an antihypertensive, much less with telmisartan.

Fourth, the teaching of Bohm *et al.* is confined to a combination of telmisartan with the ACE inhibitor ramipril, i.e., to two active ingredients acting on the renin-angiotensin system but not on HMG-CoA reductase.

Fifth, Cecil's Textbook of Medicine neither mentions telmisartan nor atorvastatin.

Finally, neither De Gasparo *et al.*, Robl *et al.*, Weinan *et al.*, Cecil's Textbook of Medicine, Harlan *et al.*, nor Bohm *et al.* teach or suggest that telmisartan increases the expression of genes regulated by the PPARgamma receptor, i.e., an activity known from antidiabetic drugs, which is the reason that telmisartan is a preferred combination partner for atorvastatin in the treatment of, e.g., diabetes, and this metabolic activity appears to be unique for telmisartan and is not recognized in the prior art. Indeed, De Gasparo *et al.* teaches the use of AT_1 receptor antagonists of "differing structural features" and therefore suggests that the specific chemical structure is of no concern and none of the other art cited makes up for this defect.

Furthermore, neither Harlan *et al.* (disclosing an aerosol formulation of statins) nor Bohm *et al.* (disclosing a combination of telmisartan with ACE inhibitors) disclose, suggest, or hint at telmisartan combinations with statins and it is unclear why or how one of skill in the art at the time the claimed invention was made would combine their teachings with De Gasparo *et al.* Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner also again provisionally rejected claims 2 and 7 to 18 for nonstatutory obviousness-type double patenting over claims 1 and 8 to 35 of U.S.S.N. 10/757,015, in view of Harlan *et al.*; provisionally rejected claims 14 to 18 for nonstatutory obviousness-type double patenting over claim 18 of U.S.S.N. 10/899,784; and provisionally rejected claims 14 to 18 for nonstatutory obviousness-type double patenting over claims 1 to 17 and 22 of U.S.S.N. 11/300,947 in view of De Gasparo *et al.*

In response, applicants undertake to file a terminal disclaimer with respect to U.S.S.N. 10/757,015, U.S.S.N. 10/899,784, or U.S.S.N. 11/300,947, if (1) the instant claims be found otherwise allowable, and (2) applicants determine that such application poses a double patenting issue at that time. Since the scope of the claims may change and moot these provisional rejections, there is not need to address these issues at this time. Accordingly, applicants again respectfully request that the Examiner withdraw these provisional rejections for consideration later.

Applicants submit that all the pending claims are allowable and respectfully solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Respectfully submitted,

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